



**Severe drug allergy:
the first 100 cases reported
to the Allergy Vigilance Network**

G. Kanny (Nancy), E.Beaudouin (Remiremont), P.Demoly (Montpellier), L Guenard (Strasbourg), C Ponvert (Paris), JL.Grand (Liege), C Gallen (Narbonne), P.Chalmet (Montluçon), A Croizier (Nancy), JP.Jacquier (Chambéry), M.Morisset (Nancy), A.Auffret (Angers), V.Cordebar (Nancy), C.Debavelaere (Boulogne sur Mer), JM.Devoisins (Cholet), C.Nootens (Bruxelles), N.Petit (Nancy), F. Pirson (Bruxelles),A Sorlin (Berck Sur Mer), Dr A.Andrier Schmitt (Thonon les Bains), I.Bossé (La Rochelle), M.Buard (Rennes), C.Chappard (St Etienne), F.Codreanu (Nancy), S.Delauney (Nouméa), F Delepouille (Dunkerque), B.Dubegny (Laval), Y.El Guedarri (Maroc), MF Fardeaux (Aix en Provence), J.Gayraud (Tarbes), JL Hallet (Luneville), J.Lesellin (Angers), F.Louis Donguy (Nice), JP Mallet (St Nazaire), H Masson (Bordeaux), ML Paquin (Pontarlier), JM.Rame (Besançon), I.Sullerot (Sens), DA.Moneret-Vautrin (Nancy)

Data treated and collected by L.Parisot

Allergy Vigilance Network
Internal Medicine, Clinical Immunology and Allergology, University Hospital
54035 Nancy Cedex, France

Abstract

Rationale: The Allergy Vigilance Network, made up of 326 allergists collects cases of severe allergic reactions.

Methods: The cases are reported on line (<http://www.allergovigilance.org>), by e-mail (l.parisot@chu-nancy.fr) or fax (03-83-85-28-64).

Results: 100 severe allergic drug reactions have been collected by the 15th July 2004: 41 males, 59 females, mean age 42 ± 17 years (4 to 78 years). The clinical features are: anaphylactic shock (65 cases), anaphylactoid shock (4), laryngeal edema (5), systemic reaction (16), generalized urticaria (8), facial oedema (1), severe acute asthma (1). Epinephrine was used 40 times. An emergency medical unit was required 41 times, hospitalization in 46 cases. The etiological diagnosis is based on clinical history and pharmacological imputability criteria for 15 patients, skin tests (71), biology (7), challenge tests (10).

Incriminated drugs are: antibiotics [amoxicillin (40 including 1 death), cephalosporin (15), quinolones(3), bacampicillin, vancomycin (1)]; NSAID (11); paracetamol (5) ; curare (6), hymenoptera venom immunotherapy (3); anatoxin diphtheria (2), tetanus (1); latex (2); iodinated contrast media (2); ondansetron, carboxymethylcellulose, noramidopyrin, heparin, chestnut, *Viscum album*, synthetic gelatin, pholcodin (1)

Conclusions: The Allergy Vigilance Network represents a great advance in the collection and evaluation of severe drug allergy. It allows a better understanding and command of allergy risk. The first 100 reported cases underline the great variety of incriminated drugs, among which antibiotics represent 60%, especially penicillins (40%). The possibility of establishing a precise diagnosis by non-invasive tests seems quite essential to propose targeted avoidance. This justifies the entire interest in pharmacovigilance in addition of classical imputability criteria.

Adverse reactions to drugs constitute a main public health problem. They concern 6 to 15% of hospitalized patients (1). Approximately 6 to 10 % of these adverse effects are due to an allergic mechanism (2). Moreover, drug allergy is one of the main three causes of anaphylactic shock, as well as food and hymenoptera stings.

The importance of this problem, the lack of epidemiological data and of diagnostic criteria led in May 2002 to the setting up of a system of collecting data of severe drug allergic reaction in may 2002 by the Allergy Vigilance Network (3). We report the first 100 cases of severe drug allergic reactions, which have been collected over this 2 years period up to July 2004.

Materials & methods

The Allergy Vigilance Network was created in 2001. It composed 326 allergists who report severe allergic reactions following allergy assessment. The membership to the Allergy Vigilance Network is free on a voluntary basis. Communication is established by e-mail. The cases are communicated to all members of the Allergy Vigilance Network and published both in the section of Medic'Inter of the journal Alim'Inter and on the website. The analysis of collected data are performed twice a year

The data are collected on a standardized form in which the doctor's identity, the clinical feature of the reaction, the modalities of emergency treatment, the results of allergy check-up and the final diagnosis retained are specified. The declaration can also be made on line on the website : <http://www.allergovigilance.org> in three languages : French, English and Spanish

On July 2004 the Allergy Vigilance Network composed 326 members : 199 allergists, 10 internists, 41 pediatricians, 43 pneumologists, 12 dermatologists, 10 biologists and 12 institutional links.

A case of drug allergy has been considered as severe if the emergency intervention of a physician was required.

This declaration is complementary of the declaration to the regional center of pharmacovigilance.

Results

39 allergists have reported the first 100 cases of severe drug allergic reactions. The declaration is in continuing increase (figure 2).

These observations concern 41 males and 59 females. The mean age is 42 ± 17 years [4-78 years].

The clinical features are 65 anaphylactic shocks, 4 anaphylactoid shocks, 5 laryngeal edemas, 16 systemic reactions, 8 generalized urticarias, 1 facial edema, 1 acute asthma.

In 81 cases, medical intervention was initiated by a third person. Emergency units were required in 31 cases. An hospitalization was required in 46 out of 81. Epinephrine was used 45 times.

19 cases have occurred during anesthesia.

An associated drug intake is noted as an associated factor : β -blockers (8), angiotensin converting enzyme inhibitors (2), angiotensin-2-receptors antagonist (1), non-steroidal anti-inflammatory drug (1).

The diagnosis was established exclusively on history and pharmacologic criteria of imputability in 19 patients.

Skin tests were performed in 81 patients and were positive in 71 out of them: 39 prick-test and 32 intradermal tests (table 1).

Biology confirmed skin tests in 6 cases : Rast penicillin G (2), Rast latex (1), RAST tetanus anatoxine (1), sIgE to paracetamol (1), leukocyte histamine release test to *viscum album*, leucotrienes release test to ketoprofen in the context of laryngeal edema. A case of allergy to paracetamol was documented by sIgE and positive oral challenge test (144 mg).

In 10 cases, the skin testing was negative and the diagnosis was confirmed by oral challenge tests : paracetamol (3), niflumic acid (1), piroxicam (1), cefpodoxime (1), amoxicillin (1), amoxicillin-clavulanic acid (1), cefaclor (1), and labial challenge test to nabumetone (1).

The incriminated drugs are multiple. Antibiotics were incriminated in 58% of cases. Amoxicillin was predominant (35/58 i.e. 60%). For amoxicillin, diagnosis was confirmed by prick-tests in 17 cases, at a concentration of 0.1 μ g/ml to 100 mg/ml, by intradermal tests (IDT) in 16 cases, at a concentration of 0.25 mg/ml to 25 mg/ml. In only one case, the challenge test was positive with negative skin tests.

Non steroidal anti-inflammatory drugs and muscle relaxants represent respectively 13% and 6% of the reported cases. The drugs incriminated during anesthesia (19% of cases) were antibiotics (9/19), muscle relaxants (6/19), latex (1), synthetic gelatin (1), ketoprofene (1), ondasetron (1).

The frequency of severe reactions to paracetamol reached 5%. One reaction was due to an IgE mechanism with positive skin prick-tests and sIgE. In three cases, the allergy check-up was negative and the diagnosis could be established only by oral challenge tests positive to low doses: reactogenic doses are : 6, 144 and 500 mg.

Drugs incriminated are:

- Antibiotics (58) : amoxicillin (23 cases out of one death) et amoxicillin + clavulanic acid (12), bacampicillin (1), cefatrizine (4), cefaclor (3), cefamandole (1), cefazoline (3), cefuroxime (2), cefoxitine (1), cefpodoxime (2), ceftriaxone (2), pristnamycine (1), vancomycine (1), ofloxacin (1), moxifloxacin (2),

- NSAID (13): aspirin (2), ketoprofene (2), diclofenac (1), tenoxicam (1), celocoxib (1), ibuprofene (3), niflumic acid (1), naproxene (1), nabumetone(1)
- Muscle relaxants (6) : suxamethonium (3), atracurium : (1), rocuronium (2)
- Paracetamol (5)
- Hymenotera venum: 3 specific immunotherapies
- Iodinated contrast media (2): ioxaglic acid (1), iobitridol (1)
- Anatoxine (2) : diphteria (1), tetanus (1)
- Latex (2)
- Ondansetron (1)
- Carboxymethylcellulose (1)
- Noramidopyrine (1)
- Heparin (1)
- Chestnut (1)
- *Viscum album* (1)
- Methylprednisolone (1)
- Gelatin (1)
- Pholcodine (1)

In 3 cases, a systemic reaction was induced by skin tests : 1 case due to IDT with amoxicillin at 0.1 mg/ml, one due to an IDT with PPL at 2.5 mg/ml and 1 case due to an IDT with suxamethonium. In these 3 cases, allergists used epinephrine and corticoids with a favorable evolution.

Discussion

The continuing increase of declarations of severe drug allergic reactions reflects the importance of this diagnosis in daily allergology practice. These first 100 cases reported to Allergy Vigilance Network allow us to draw the clinical profile of severe drug allergic reaction and to evaluate the pertinence of the allergy assessment in these cases.

The analysis reveals the high diversity of the incriminated drugs. Antibiotics, particularly β -lactamins and penicillins respectively represent the most often incriminated drugs: 58%, 53% and 36% of cases, which correspond to previously published data (4, 5). NSAIDs are second in frequency, representing 13 % of reported reactions, followed by muscle relaxants (6% of reported cases). The increasing role of antibiotics in per-anesthesia anaphylaxis have previously underlined by epidemiological survey of GERAP (study group of anesthesia anaphylactoid reactions) (6)

It is important to underline the frequency of severe reactions to paracetamol (5%). Their mechanism seems to be complex : one reaction was due to an IgE mechanism and in three cases, the allergy check-up was negative and the diagnosis could be established only by oral challenge tests positive to low doses. This high reactivity is due to a non-elucidated mechanism.

The other incriminated drugs are various: active ingredients, like heparin, vaccines, immunotherapies, drug excipients and phytotherapy ingredients like *viscum album*.

The interest of allergy assessment is essential to identify the incriminated drug . Skin tests confirmed the diagnosis in 88% of cases (71/81), challenge tests for 12% of patients (10/81), biological tests in 10% (8/81). It is important to note that in the 9 patients who have undergone of skin and biological tests, the concordance is observed in 66% of cases.

The possibility to establish a precise diagnosis using non-invasive tests, such as skin and biological tests, appears to be essential for targeted avoidance strategies. Skin tests targeted the etiology in 88% of cases and prick-test alone in 54% of cases. The risk of anaphylactic reaction with IDT underlines the need of beginning the check-up with prick-tests at low concentrations. The validation of diagnostic procedures is required. The increasing precision of information contained in the allergists' declaration will allow us to validate diagnosis procedure using the convergence and multicentric validation of methodology. This validation allows the study of cross-reactivity which depends on the molecular structure and not on the pharmacological action. The challenge tests represent the only way to diagnose certain drug intolerance, such as NSAID intolerance, which responds to a pharmacological mechanism and not immunologic (7).

These allergy tests merited the attention of the pharmacovigilance institution : they must be considered in addition of classical criteria of imputability which are chronologic, semiologic and bibliographic (8).

Conclusion

The frequency of severe drug allergic reactions justifies the validation of optimal diagnostic strategies. The Allergy Vigilance Network seems to be an essential tool to collect epidemiologic data and to validate diagnostic procedures in order to offer all patient wherever they live an optimal management of their drug allergy and personalized therapeutic strategies. In this view, the convergence of observations coming from members of Allergy Vigilance Network constitutes considerable progress in the study of drug allergy and, leads to a better knowledge of this main public health problem.

References

1. Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: meta-analysis of prospective studies. *JAMA* 1998;15:1200-1205.
2. Gruchalla RS. Drug allergy. *J Allergy Clin Immunol* 2003;111:S548-S559.
3. Moneret-Vautrin DA, Grosdidier R, Trechot P, Netter P, Gérard H. Diagnostic des réactions allergiques et pseudo-allergiques médicamenteuses chez 55 patients: concept d'allergo-vigilance. *Rev Fr Allergol* 1989;29:7-13.
4. Hunziker T, Künzi UP, Braunschweig S, Zehnder D, Hoigné R. Comprehensive hospital drug monitoring (CHDM): adverse skin reactions, a 20-year survey. *Allergy* 1997;52:388-393.
5. Yu-Hor Thong B, Leong KP, Tang CY, Nursing B, Chng HH. Drug allergy in a general hospital: results of a novel prospective inpatient reporting system. *Ann Allergy Asthma Immunol* 2003;90:342-347.
6. Mertes PM, Laxenaire MC, Alla F. Groupe d'études des réactions anaphylactoides peranesthésiques. *Anesthesiology* 2003;99:521-523.
7. Messaad D, Sahla H, Benahmed S, Godard P, Bousquet J, Demoly P. Drug provocation tests in patients with a history suggesting an immediate drug hypersensitivity reaction. *Ann Int Med* 2004;140:1001-1006.
8. Bégaud B, Evreux J, Jouglard J, Lagier G. Imputabilité des effets inattendus ou toxiques des médicaments. Actualisation de la méthode utilisée en France. *Thérapie* 1985;40:111-118.

Table n°1 : Positive skin tests (71 drug allergic reactions)

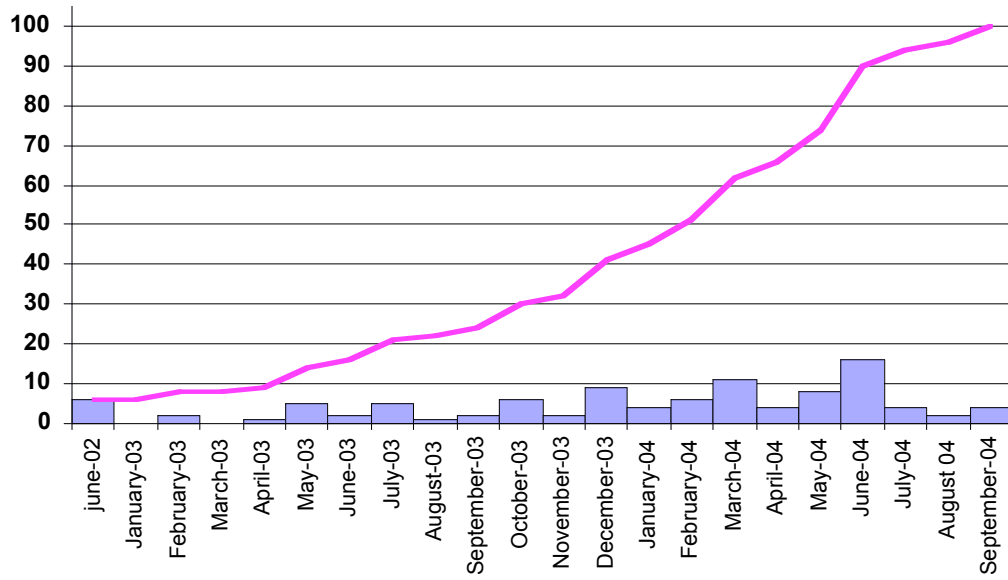
	Prick-test	IDR 10 ⁻¹	IDR 10 ⁻²	IDR 10 ⁻³
Amoxicillin	19	7	4	1
Amoxicillin + clavulanic acid	0	5	0	0
Cefaclor	2	0	0	0
Céfazoline	2	0	0	0
Cefamandole	1	0	0	0
Céfatrizine	2	1	0	0
Cefuroxime	2	0	0	0
Ceftriaxone	0	1	0	0
Vancomycine	0	0	1	0
Ofloxacin	1	0	0	0
Moxifloxacin	1	0	0	0
Cefoxitine	1	0	1	0
Paracetamol	1	0	0	0
Diclofenac	0	1	0	0
Ioxaglic acid	0	1	0	0
Iorbitridol	0	1	0	0
Ondansetron	0	0	1	0
Pholcodine	1	0	0	0
Suxamethonium	2	0	1	0
Rocuronium	0	1	0	0
Diphtheria anatoxin	0	0	0	1
Tetanus anatoxin	0	1	0	0
Noramidopyrine	1	0	0	0
Calciparine	1	0	0	0
Viscum album	0	0	0	1
Latex	1	0	0	0
Gelatin	0	0	0	1
Total	38	21	8	4

Table 2 : Concordance of skin tests (ST) and biological tests (BT) in reported drug allergy reactions (9 cases)

	ST + BT +	ST + BT -	ST - BT +	ST - BT -
Penicillin	2	2	0	0
Anatoxine	1	0	0	0
Ketoprofene	1	0	0	0
Latex	1	0	0	0
Paracetamol	0	0	1	0
<i>Viscum album</i>	1	0	0	0
Total	6	2	1	0

Figure 1 : Calendar of declarations of severe drug allergy to the Allergy Vigilance Network

cases (n)



Declaration severe allergic reaction

Date :

Doctor's name: e-mail: Town:

:

sex, age, type of the clinical reaction:

Medical management:

Past history :

Allergy check-up (skin, biological and challenge tests):

Associated factors :

Particular comment :

Diagnosis :

The completed form will be returned to :

Allergy Vigilance Network

Internal Medecine, Clinical Immunology and Allergology

Hôpital Central, 54035 Nancy cedex France

e-mail : L.parisot@chu-nancy.fr

fax : 03.83.85.28.64

Déclaration en ligne : <http://www.allergovigilance.org>